

Connectivity of human brain measured with TMS and EEG

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1 Introduction

With focal transcranial magnetic stimulation (TMS), it is possible to activate cortical neurons non-invasively. Simultaneously, variations in scalp potential due to neuronal activation can be detected with electroencephalography (EEG). The stimulation of neurons is actually due to the induced electric field, which is strongest in the superficial cortical layers [1]. How this field interacts with neurons of different sizes and shapes in varying chemical environments and amidst ongoing physiological events, is poorly known.

TMS together with EEG provides a time-resolved method offering information about area-to-area conduction, i.e., connectivity, between brain areas [2]. Connectivity-related phenomena are observed in 30 milliseconds post-stimulus. Connectivity analysis requires that the sources of the measured potentials are estimated, e.g., with the minimum-norm current-density distribution [3].

In this paper, we will describe how transcallosal conduction times are determined utilizing activation maps, derived from EEG recorded during TMS experiments. We use the electrophysiological reasoning that the rate of the current-density change in any cortical area is largest during the onset of neuronal firing. When the maximal activation is reached, the rate of the current-density change slows down to zero. We also trace the activation spread post-stimulus and discuss the physiological explanation of the observed spatial activation patterns.

2 Methods

2.1 Subjects

Six healthy, right-handed volunteers (2 females, 4 males; 23–72 years of age; mean 37) were studied. All subjects gave a written informed consent for the study.

2.2 Transcranial magnetic stimulation

Five sites of the left frontal and anterior parietal cortices within an area of 3 cm² were stimulated. A figure-of-eight-shaped coil was used for stimulation and was kept above the subject's head with a mechanical holder. Stimulation point 1 was selected so as to maximize the motor response from the right abductor digiti minimi muscle. This point and four points at a distance of 1 cm around it were targeted with a sequence of 120 magnetic pulses, delivered at an inter-stimulus interval of 1.5–2.5 s. Stimulation experiment was repeated to Subjects 3–6 after a break of 2–5 minutes.

2.3 Electroencephalography

A stretchable cap with sixty Ag/AgCl-coated C-shaped silver electrodes was used for recording EEG. Signals, referenced to an additional electrode on the forehead, were low-pass filtered with a fourth-order Bessel filter (0.1–500 Hz) and sampled at 1450 Hz with 16-bit resolution [4]. With a sample-and-hold circuit, saturation of the amplifiers was avoided during the TMS pulse and until 7 ms post-stimulus.

2.4 Data analysis

Post-processing of the EEG was performed with MATLAB (The Mathworks, Inc., Natick, MA, USA). About 100 epochs from 100 ms pre-stimulus to 100 ms post-stimulus were averaged after rejection of noisy data. The signals were band-pass filtered with a digital 96th-order Hamming window (pass bands 0–44 and 58–250 Hz) to suppress the disturbance of the mains voltage and to cut off high-frequency noise.

To examine the rate of potential changes ($\partial V/\partial t$), the signals were differentiated as a function of time. In this way, the effect of baseline distortions in the raw EEG was suppressed in further analysis. From the differentiated data, maps expressing the spatial distribution of the rate of scalp potential changes were derived.

Based on the differentiated potentials, the bioelectric inverse problem was solved with the minimum-norm estimate (MNE) [3], giving the rate of current-density change ($\partial CD/\partial t$). The MNE was calculated using a spherical model of the head, consisting of four concentric layers of different conductivities (scalp, skull, cerebrospinal fluid, and brain).

The spread of cortical activation was deduced by reviewing the spatiotemporal distribution of $\partial CD/\partial t$. The examination was performed on the basis of the distribution displayed on a computer screen on a two-dimensional projection of the spherical surface representing the head (Fig. 3). The data were reviewed with 0.7-ms intervals from 0 to 30 ms post-stimulus. The sphere surface was divided to frontal and parietal regions based on the coordinates of stimulation point 1, which was likely situated adjacent to the central sulcus.

3 Results

3.1 TMS-evoked EEG waveforms

The TMS-evoked EEG response and its derivative, measured with a contralateral electrode approximately above the primary motor cortex, are illustrated in Fig. 1 for Subject 4. The following peaks were found in the average response (measured with the same electrode) calculated over all subjects 0–50 ms post-stimulus: N20, P32, N37, and P46.

In Fig. 2, responses from three stimulation trials are shown, illustrating the similarity of the waveforms when different sites were stimulated or when the stimulation was repeated to the same target, although some variance in amplitudes was observed (the same electrode and subject as above).

3.2 Activation distributions

Ipsilateral activation was detected near the coil center at 7 ms post-stimulus, when the amplifier outputs were unlocked, the maximal activation extending to an area of several centimeters in frontal and anterior parietal regions. In 23/50 trials (in 6 subjects), a clearly lateral maximum was observed at 17 ± 5 ms (mean $\pm$ SD).

Clear connectivity of the corresponding cortical regions in the two hemispheres was found (in 47/50 trials; signals from three trials were artifactual). At 20 ± 2 post-stimulus, contralateral cortical activation was detected for the first time. In 25/47 trials (in 6 subjects), the maximal contralateral activation was observed in the frontal lobe and in 18/47 trials (in 5 subjects), in the parietal lobe. In 4 trials, maximums were found in both the frontal and parietal regions.

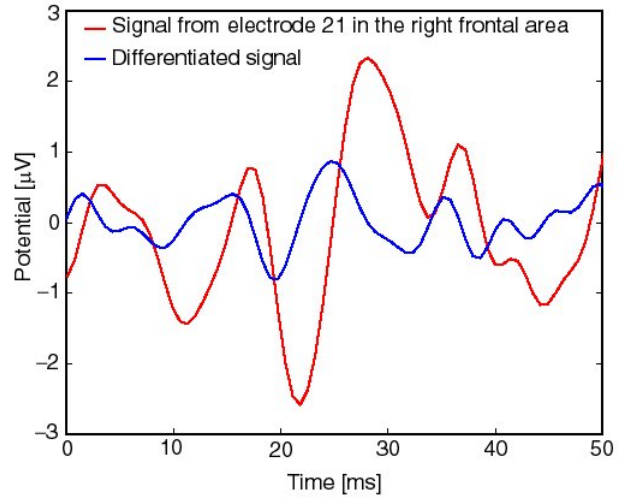


Figure 1: EEG response and its derivative 0–50 ms post-stimulus measured with a contralateral electrode (electrode 21) approximately above the primary motor cortex (reference on the forehead). Dominant negative potential peaks were found at about 20 and 35 ms and dominant positive peaks at about 15 and 30 ms. Subject 4.

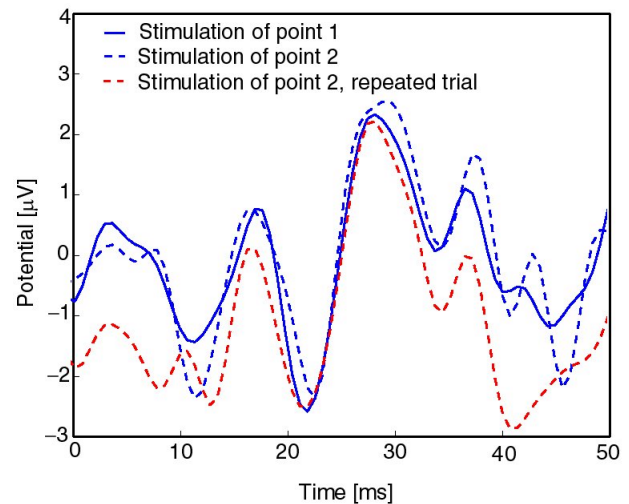


Figure 2: EEG responses from three different trials 0–50 ms post-stimulus, measured with the same electrode as in Fig. 1 (Subject 4). The solid curve plots the EEG response when point 1 was stimulated. The dashed curves are responses to repeated stimulations of point 2. Note the similarity of the waveforms between two stimulation targets and the repeated stimulations to the same target.

No differences (within measurement accuracy) were found between conduction times when different points were stimulated (point 1: 20 ± 1 ; point 2: 19 ± 2 ; point 3: 22 ± 2 , point 4: 20 ± 2 ; point 5: 22 ± 4). The mean difference of conduction times between repeated trials to the same target point and subject was 2 ± 2 ms. Distributions of the rate of scalp

potential and cortical current-density change at selected time points post-stimulus are displayed in Fig. 3 (Subject 3).

4 Discussion

With the combination of TMS and EEG, we have studied connectivity of the cortex and described a procedure for determining transcallosal conduction times. The analysis was performed using distributions of the rate of the cortical current-density change, reflecting the local intensity of neuronal interaction in the cortex, as information is mediated in the form of electrical impulses through neuronal firing. We reached an accuracy of one millisecond in determination of the conduction times.

The activation patterns observed were in agreement with the known connections of the cortex [5]. The primary motor area is ipsilaterally connected with the premotor cortex, the supplementary motor area, and the primary (S1) and secondary (S2) somatosensory cortices. S1 is connected with the posterior parietal cortex (PPC), as well as the above mentioned motor areas and S2. These were probably the dominant pathways mediating the intracortical activation. The intercortical activation spread was conducted by transcallosal white matter tracts, traversing the corpus callosum. The lateral extension of the ipsilateral activity could be due to activation of S2 or auditory cortices and the parietal extensions of the ipsi- and contralateral activity due to the connection of S1 with PPC.

The connectivity of the brain was studied with TMS and EEG for the first time in 1997 [2]; activation was found in the contralateral cortex in about 20 ms post-stimulus. Transcallosal conduction times ranging from 4 to 20 ms have been obtained with TMS combined with the measurement of electromyographic (EMG) activity from muscles [6,7]. Our conduction times are in agreement with these results.

TMS and simultaneous EMG recording from muscles is an indirect method for measuring transcallosal conduction, and it is not applicable to any other connectivity studies than those associated with motor activity. TMS together with positron emission tomography (PET) was applied to the study of connectivity first in 1997 [8]. The disadvantage of PET is its indirectness; it measures changes in the cerebral blood flow, occurring from tens to thousands of milliseconds after neuronal firing. The technique gives practically no temporal information about connectivity, the time scale of which is only some tens of milliseconds.

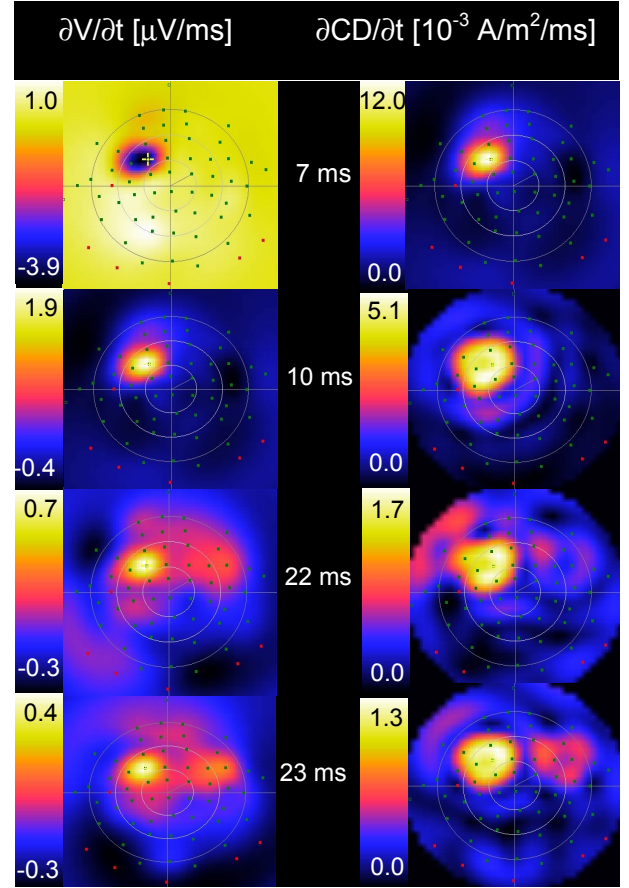


Figure 3: Activation spread at selected time points post-stimulus, expressed through maps of the rate of change of scalp potential (left) and cortical current density (right) in Subject 3. The surface of the spherical head model was projected into two dimensions (anterior direction = above; posterior direction = below). The activation appeared to spread from below the coil to the surrounding cortical areas and to the contralateral cortex at 22 ms. The contralateral current-density change speeded up until 23 ms. The sites of the maximal rate of the cortical current-density change correspond to extensive neuronal firing. The potential is given in $\mu\text{V/ms}$ and current-density change in $10^{-3} \text{ A/m}^2/\text{ms}$.

TMS and EEG provides a very good temporal resolution and is not restricted to investigation of pure motor functions. The spatial resolution appears adequate for deducing connectivity between areas of a few centimeters in diameter, depending mainly on the size of the computation space of the MNE, the number of electrodes, and the signal-to-noise ratio. In conclusion, with TMS and EEG it is possible, not only to evoke brain activation non-invasively, but also to trace the spreading activation in the cortex with a temporal resolution of one millisecond. Based on the activation patterns, one can deduce the

connectivity of adjacent and contralateral brain areas. TMS together with EEG provides a new modality for spatiotemporal characterization of neuronal function in the human brain.

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